

**REMARKS**

Reconsideration of this application is respectfully requested.

Claims 2-24 and 245-302 were previously pending in this application. Claims 252, 258, 273-275, 278, 289-290, 292-293 and 296 have been amended. Claims 2-24 have been canceled above. No claims have been added by this paper. Accordingly, claims 245-302 as amended above are presented for further examination.

The first page (line 1) of the specification has been amended by inserting information cross-referencing this divisional application with the prior parent application, Serial No. 08/574,443, filed on December 15, 1995. The parent application was revived for purposes of continuity so that the present divisional application could be filed.

Several informalities in the specification have been corrected. These include changes on pages 9, 64, 105, 109, 114, 123, 127, 134, 151, 159, 180 and 181.

For the sake of clarity and definiteness, relatively minor changes to claims 252, 258, 273-275, 278, 289-290, 292-293 and 296 have been effected above. All of these minor changes affect only the Markush language in the foregoing claims. It is believed that the amended claim language in these claims conforms to the accepted proper usage under U.S. patent practice.

Entry of the claim amendments is respectfully requested.

**Objection to Patent Drawings**

Acknowledgement is made of the Notice of Draftperson's Patent Drawings Review that was issued in connection with this application. Formal drawings will be submitted as soon as allowable subject matter has been

indicated in this application.

**Submission of Sequence Listing**

Applicants are filing concurrently with this Amendment a response to the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

**The First Rejection for Double Patenting Under 35 U.S.C. §101**

Claims 2-24 stand provisionally rejected under 35 U.S.C. §101 as claiming the same invention of claims 2-24 of copending Application Nos.: 08/978632, 08/978636, 08/978634, 08/978635, 08/978637, 08/978638, 08/978639 and 08/574,443. In the February 16, 1999 Office Action (page 2), the Examiner noted that "[t]his is a provisional double patenting since the conflicting claims have not in fact been patented."

As indicated above, claims 2-24 have now been canceled as they should have been when claims 245-302 were presented in Applicants' November 24, 1997 Preliminary Amendment. Any inconvenience caused by this oversight is sincerely regretted.

In view of the cancelation of claims 2-24, Applicants respectfully request withdrawal of the double patenting rejection

**The Second Rejection for Double Patenting Under 35 U.S.C. §101**

Claim 245 stands provisionally rejected under the judicially created doctrine of double patenting over claims 22-24 of the instant application and of copending Application Nos. 08/978,632, 08/978,634, 08/978,635, 08/978,636, 08/978,637, and 08/978,638. The Examiner's remarks are set forth on pages 3-4 of the February 16, 1999 Office Action.

With the cancelation of claims 2-24 above, it is believed that this ground of rejection for obviousness-type double patenting has been rendered moot and irrelevant. Withdrawal of the provisional rejection of claim 245 is respectfully requested.

**The Rejection Under 35 U.S.C. §112, Second Paragraph**

Claims 2-21 and 256-260 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the Office Action (page 4), the Examiner stated:

Claims 2-21 are indefinite because they depend from canceled claim 1. Therefore, claims 2-21 do not depend on any independent claim.

It is not clear what the metes and bounds are of the language "a specific complex" is in claims 256-260.

The first point listed above with respect to claims 2-21 is believed to have been rendered moot by the cancelation of those claims.

With respect to the second point, it is believed that the term "specific complex" is proper claim language in light of Applicants' disclosure and its meaning in the art. Claim 256 recites "[t]he composition of claim 255, wherein said noncovalent binding comprises a specific complex." Claims 257 and 258 depend from claim 256 and recite:

"wherein said specific complex is mediated by a ligand binding receptor" (claim 257); and

"wherein said ligand binding receptor is selected from a polynucleotide sequence to be recognized by its complementary sequence, an antigen to be recognized by its corresponding monoclonal or polyclonal antibody, an antibody to be recognized by its corresponding antigen, a lectin to be recognized by its corresponding sugar, a hormone to be recognized by its receptor, a receptor to be recognized by its hormone, an inhibitor to be recognized by its enzyme, an enzyme to be recognized by its inhibitor, a cofactor to be recognized by its cofactor enzyme binding site, a cofactor enzyme binding site to be recognized by its cofactor, a binding ligand to be recognized by its substrate, or a combination of the foregoing"

(claim 258).

Applicants also explain the nature of the specific complex on page 56 in their specification:

. . . In addition the noncovalent binding can comprise a specific complex, e.g., a specific complex mediated by a ligand binding receptor. The ligand binding receptor can itself take a number of forms. Suitable but not necessarily limited to these members are a polynucleotide sequence to be recognized by its complementary sequence, an antigen to be recognized by its corresponding monoclonal or polyclonal antibody, an antibody to be recognized by its corresponding antigen, a lectin to be recognized by its corresponding sugar, a hormone to be recognized by its receptor, a receptor to be recognized by its hormone, an inhibitor to be recognized by its enzyme, an enzyme to be recognized by its inhibitor, a cofactor to be recognized by its cofactor enzyme binding site, a cofactor enzyme binding site to be recognized by its cofactor, a binding ligand to be recognized by its substrate, or a combination of the foregoing.

It is respectfully submitted that the skilled artisan reading Applicants' claims and disclosure would readily appreciate and comprehend the meaning of the term "specific complex" in the claims, particularly in light of the sheer vast number of examples for the "specific complex" and its subgenus "ligand binding receptor, both being given in the above-quoted passage.

In view of the above cancelation of claims 2-21 and the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection.

**The Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 2-24 and 245-302 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the Office Action (pages 5-12), the Examiner stated:

The constructs taught in the claims 2-24 are broadly drawn to a multitude of possible nucleic acid based constructs for use in a cell to produce a product (and in any context, *in vivo* or *in vitro*), comprising:

(1) the construct as linear or circular, (2) the construct as comprising 1,2 or 3 strands, (3) comprising a terminus, a polynucleotide tail which can hybridize, (4) composed of RNA or DNA or combinations, (5) containing chemically modified nucleotides or analogs, (6) containing non-nucleic acid entities composed of polymers or ligands or a combination, (7) further specifying the natural and synthetic polymers, the synthetic homo- or heteropolymer with a net charge, (8) the construct imparting a "further biological activity" by the modified nucleotide, analog, entity, ligand or combination of those, further defined as nuclease resistance, cell recognition, cell binding, and cellular or nuclear localization or a combination, (9) a ligand attached to one of the modified nucleotides, etc. of claim 1, further described as attached to a "segment" or "tail" of the construct, and further defined as being a macromolecule or small molecule or combination. Claims 22-24 describe a second construct "which when present in a cell produces a product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand."

Claims 245-254 are drawn to another broad genus of nucleic acid constructs for co-expression of a non-native polymerase and another nucleic acid sequence from the construct in a cell, again in any context, *in vivo* or *in vitro*. Dependent claims include the limitations: (1) a recognition site for the polymerase, (2) where the recognition site is complementary to a primer for the polymerase, (3) where the primer is tRNA, (4) where the polymerase is DNA polymerase, RNA polymerase, reverse transcriptase, or a combination, (5) where the RNA polymerase is a bacteriophage RNA polymerase, either T3, T7, SP6 or a combination, (6) a promoter for the RNA polymerase, (7) the nucleic acid produced is DNA, RNA, or a hybrid, chimera, or a combination and is sense or antisense DNA or RNA.

Claims 245-246 are broadly drawn to a construct for production of a product in a cell having a tail hybridized to an antibody and also having a covalently or hydrophobically bound entity with a chemical modification or a ligand.

Claims 247-266 are drawn to a composition having a "non-natural entity" of two "domains," one to a nucleic acid and the second to a cell of interest, and where the domains are not the same. The dependent claims further specify: (1) a binder which can or cannot be the same as one of the domains, and can be a polymer, matrix, support, or combination, (2) the nucleic acid can be a single nucleic acid, a nucleic acid construct, conjugate, virus, viral fragment, viral vector, viroid, phage, plasmid, vector, bacterium and fragment, or combination, (3) the domains can be attached covalently, non-covalently, or through a binder or a combination, (4) interaction with a ligand binding receptor (see claim 258), (5) binder attached by a "means other than a natural binding site" and consisting of modified fibronectin or polylysine or both, (6) and methods and a kit for administering the parent composition to a cell *in vivo* and *ex vivo*.

Claims 267-284 are drawn to an analogous invention as that of claims 247-266 but specifying "an entity" having "at least one domain to a cell of interest" attached to a non-double stranded nucleic acid component.

On pages 7-9 of the Office Action, the Examiner went on to further state:

Claims 285-302 are further drawn to an analogous invention as that of claims 247-284, but specifying "an entity" having "a domain to a nucleic acid component wherein said domain is attached to a cell of interest."

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

Furthermore, vectors ultimately designed for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon, the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and

the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multi cassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional comments follow on pages 10-12 of the Office Action where the Examiner stated:

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retro virus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to a complementary polynucleotide sequence. Likewise, claims 245-302 read on any construct for production of a product in a cell having (1) a polynucleotide terminus bound to an antibody, and having an entity comprising a chemical modification or ligand bound to the construct, or (2) "entities" having "domains" with nucleic acid and/or cell "components." The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed.

The specification fails to provide guidance for the breadth claimed since the claims vaguely claim "constructs" which "produce products." The specification does not teach by example, other than prophetically, use of any nucleic acid constructs having one or more domains for cell interaction (claims 247-302), nor methods or kits for using such a construct. Nor does it teach a construct with a polynucleotide tail with an antibody bound and also bound to an entity having a chemical modification or a ligand (claims 245-246). The specification teaches only by way of example HIV inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo*: it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of teaching of these factors in inhibition of the target, coupled to the amount of "trial and error" experimentation involved in the deduction of these results would lead one skilled in the art to necessarily practice an undue amount of experimentation *in vivo*.

No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend.

Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

The enablement rejection is respectfully traversed.

With respect to the application of the enablement rejection to claims 2-24, such grounds have been rendered moot, of course, by the cancelation of these claims.

With respect to claims 245-302, it is respectfully submitted that the subject matter of these claims is fully enabling such that a person skilled in the art could practice, without undue experimentation, Applicants' claimed invention.

As acknowledged in the Office Action, the specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Among these are several CHENAC constructs (see Figures 1-13), antibody based constructs (Figures 14-21) and multimeric insulin (Figures 22-23). Other embodiments include vectors designed for antisense inhibition of HIV in cells by coexpression of antisense DNA under control of a T7 promoter with a T7 polymerase (Figures 24-49) and plasmids containing antisense segments introduced into the transcript region of the U1 gene. Also taught in Applicants' disclosure are other multi-cassette constructs, such as TRI 101 (an M13 phage containing the "A" antisense T7 operon, the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (Figure 46), and an M13 construct constructed from multi-ligation of portions of pINT-3 and the T7 promoter driven A, B and C sequences.

As also acknowledged in the Office Action, Applicants have provided examples that show antisense inhibition of HIV in infected U937 cell culture using various U1 constructs, expression of A, B and C antisense by hybridization analysis after expression of the U1 clone, and expression of the fusion product antisense A upstream of  $\beta$ -gal gene where antisense activity of the A portion caused inhibition of  $\beta$ -gal activity in lacZ assays (Figure 51). The assertion has been made that it does not appear in the specification as filed that the multicassette A, B, C and T7 polymerase construct was applied to the same HIV challenge experiments. In response, it should not be overlooked that under the law specific examples need

not be given in the specification in order to satisfy the statutory requirements for enablement. All that is required is that the disclosure be enabling, that is to say, so that a person skilled in the art can practice the claimed invention, without undue experimentation. The fact that the same experiments for the U1 constructs were not specifically applied to the multicassette A, B, C and T7 polymerase constructs does not render the latter nonenabling. Again, the operative words under the enablement statute are "undue experimentation." Armed with Applicants' original disclosure, it is submitted that the skilled artisan could have practiced the presently claimed invention without undue experimentation.

Reconsideration and withdrawal of the enablement rejection are respectfully requested.

**The Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 2-24 and 245-262, 267-280, and 285-298 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the Office Action (pages 13-14), the Examiner stated:

Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product in a cell. Claims 245-302 are further drawn to a broad scope of constructs for production of a product in a cell having (1) a polynucleotide terminus bound to an antibody, and having an entity comprising a chemical modification or ligand bound to the construct, or (2) "entities" having "domains" with nucleic acid and/or cell "components."

The claims broadly encompass "constructs" for producing a "product," or "entities" having "domains" to nucleic acid components and cell components, and it is not clear what is embraced by the claims. The claims read on vectors, genomes, cell processes like translation, transcription, etc. as "constructs" for producing "products." The language "domain" in reference to nucleic acid constructs and cells reads on *any* region distinctively marked by some physical feature of the nucleic acid or cell. For example, the region may encompass the whole cell or a small component such as a ligand

binding site to one receptor. Furthermore, the scope of "chemical modification" as used in claims 22 and 245 is not clear in relation to the construct.

The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.

Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 245-302, no vector nucleic acid constructs having antibodies or cellular "domains" are described by way of example except by prophetically.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the specification for such a broad genus of possible "constructs," coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of "construct" species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U.S.C 112 "Written Description" requirement.

Reconsideration and withdrawal of the written description rejection are respectfully requested.

In response, Applicants are mindful that working examples are not a requirement *sine qua non* for purposes of satisfying the written description statute. In fact, all that is required is that the disclosure reasonably convey to the person skilled in the relevant art that the inventors had possession of their claimed invention. Viewed under that statutory test for written description, it is respectfully submitted that Applicants' disclosure would have reasonably conveyed to one skilled in the art that the inventors had possession of their instantly claimed invention at the time this application was first filed in December 1995.

Reconsideration and withdrawal of the written description rejection are respectfully requested.

Elazar Rabbani et al.  
Serial No.: 08/978,633  
Filed: November 25, 1997  
Page 17 [Amendment Under 37 C.F.R. §1.115 (In Response  
to the February 16, 1999 Office Action - August 16, 1999)]

**The First Rejection Under 35 U.S.C. §102**

Claims 245-302 stand rejected under 35 U.S.C. §102(e) as being anticipated by Curiel et al., U.S. Patent No. 5,521,021, issued on May 28, 1996. In the Office Action (page 15), the Examiner stated:

The claimed invention is drawn to: (1) constructs for production of a product in a cell having a terminus, a polynucleotide tail, and an entity comprising a chemical modification or a ligand bound to the construct, (2) constructs having two domains, one a nucleic acid and one a domain to a cell of interest and methods and kits for introduction of said construct into a cell or organism, (3) a composition having at least one domain to a cell of interest attached to a nucleic acid in non-double stranded form and methods and kits for introduction into a cell or organism, and (4) a composition having one domain to a nucleic acid component attached to a cell of interest and methods and kits for introduction into a cell or organism.

Curiel et al. teach constructs for improved nucleic acid delivery into cells (and organisms) for production of a product (for example, antisense or ribozymes, col. 1, line 65) including adenovirus-antibody-polylysine-DNA complexes (see fig 1) which therefore have the potential to complex as 'domains'.

The first anticipation rejection is respectfully traversed.

Applicants respectfully contend that there is a lack of material identity between Curiel's patent and their instant invention as embodied in claims 245-302.

Reconsideration and withdrawal of the anticipation rejection are respectfully requested.

**The Second Rejection Under 35 U.S.C. §102**

Claims 22-24 stand rejected under 35 U.S.C. §102(e) as being anticipated by Meyer et al., U.S. Patent No. 5,574,142, issued on November 12, 1996. In the Office Action (page 16), the Examiner stated:

The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ioniically to an entity comprising a modification or a ligand, and further comprises a

hybridized polynucleotide tail.

Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

In view of the cancelation of claims 22-24 above, the rejection based on Meyer's patent has been rendered moot and irrelevant. Accordingly, withdrawal of this rejection is respectfully requested.

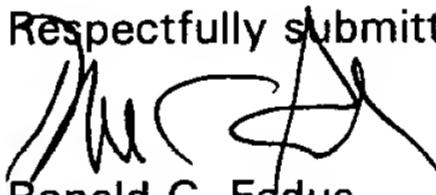
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**SUMMARY AND CONCLUSIONS**

Claims 245-302 are presented for further examination, claims 2-24 having been canceled. Claims 252, 258, 273-275, 278, 289-290, 292-293 and 296 have been amended. No claims have been added by this paper.

This Amendment is being accompanied by a Request For An Extension Of Time (3 months) and authorization for the small entity fee therefor. No other fee or fees are believed due for filing this Amendment. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,  
  
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